

Clinical issues in genetic testing for multifactorial diseases



Technological advances in genomics are shifting the genetic testing paradigm, from testing targeted mutations in selected genes to testing whole genes and even whole genomes. These exciting developments raise numerous practical pitfalls and ethical issues.

Two articles in this issue of the *SAMJ* address genetic testing for multifactorial diseases.^[1,2]

Multifactorial diseases (MDs) are those caused by the interaction of multiple genetic and environmental risk factors, and cause a huge disease burden in South Africa (SA).^[3] They include most 'lifestyle diseases', neuropsychiatric disorders, and cancer predispositions. Given the importance of MDs, detection of genetic predisposition is potentially attractive to facilitate prevention.

One preventive approach targets the 'Mendelian subsets' found within many MDs. These are single gene disorders (SGDs) that, although uncommon, are important because of the high disease burden for affected individuals and families: disease is often early onset and inheritance usually autosomal dominant. Examples include familial hypercholesterolaemia, and hereditary breast and ovarian cancer (HBOC) due to BRCA1 and BRCA2 gene mutations.

The primary caregiver should be alerted to a possible SGD by the family history or atypical features such as early onset. Further assessment follows a standard clinical genetic/genetic counselling approach. In the case of suspected HBOC, a risk assessment is conducted to decide if the cost of BRCA testing is warranted, and includes a detailed family history. Initial genetic testing is best offered to an individual with cancer – detection of a disease-causing mutation may modify treatment offered, and allows other family members to consider testing to predict their risk. In the well publicised case of Angelina Jolie, genetic counselling and testing for BRCA mutations may have come too late to save her mother, but did allow her to make difficult but potentially life-saving decisions regarding risk-reducing surgery.

In view of the personal and family implications of such SGDs, it is essential that the tests have excellent clinical validity (high sensitivity and specificity) and be provided in the context of genetic counselling by a clinical geneticist, genetic counsellor or other appropriately skilled health professional.^[4]

The article by Schoeman *et al.*^[1] describes an approach to detection of BRCA-related breast cancer in a local public health sector setting. The article is probably the first local description of a large-scale, long-term genetic counselling and testing service that is rooted in mainstream clinical practice rather than in molecular genetic research. The approach aims to maximise accessibility and cost-effectiveness of testing while still providing effective genetic counselling. Important features include: targeting individuals with cancer rather than the 'worried well'; use of local criteria for offering testing; a tiered approach to testing, with the cheaper first tier targeted at locally common mutations; adaptation of genetic counselling to local circumstances with the genetic counsellor focusing especially on positive result feedback and family follow-up; and integration of the genetics professional into the multidisciplinary team. Despite rationing of tests, the overall BRCA mutation detection rate of 2.6% (and 16% of those tested) is credible.

For the remaining majority of MDs, it is increasingly clear that the genetic component of susceptibility is usually very complex, with many genetic loci and even more genetic variants being involved, and a large contribution from environmental factors. In this context, few of

the genetic variants detected in genome-wide association studies have clinically useful predictive value for disease in a given individual. Even large panels of genetic variants lack clinical validity or utility.

The article by Dandara *et al.*,^[2] from the committee of the Southern African Society for Human Genetics (SASHG), recounts mainstream genetic opinion on direct-to-consumer (DTC) testing. It focuses primarily on testing for genetic susceptibility to MDs and highlights the lack of proven clinical validity and utility of most such tests. Like the article, this editorial makes no attempt to address the full range of DTC genetic tests.

A deficiency in the article is its definition of DTC testing as taking place 'without a healthcare provider being involved' – this excludes the situation where the test is advertised as DTC, but a healthcare provider (usually without a genetic qualification) is involved in the process. In fact, if a test makes 'health claims' but lacks clinical validity, it should not be offered in any healthcare setting. In the case of research, the research component should be clearly demarcated and receive specific consent.

As previously discussed, testing for genetic variants that cause SGDs warrants counselling by a genetically-skilled healthcare professional. This needs to be taken seriously by DTC companies offering testing panels that include known disease-causing mutations (some local DTC companies do refer for genetic counselling in this situation).

In some cases DTC tests are marketed for 'recreational' rather than health purposes, on the basis that people have a right to explore their own genomic information. However, the authors' recommendations for provision of clear information and access to genetic counselling are important if there is potential for detecting variants with health implications.

Unlike many countries, SA lacks legislation to specifically regulate 'medical devices' (including diagnostic tests) in general. In this context, the authors' suggestion that DTC genetic testing be reviewed by the Department of Health would perhaps be better placed as part of a broader review process. If the SASHG deems DTC testing a priority, an alternative approach is provided by the Consumer Protection Act, which allows interested parties to address specific issues directly with the Consumer Commission or Tribunal.^[5]

In summary, genetic healthcare professionals have an important role in both the implementation of new genetic tests and the gatekeeping process, at the dawn of the new genomic diagnostics era.

M Urban

Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

Corresponding author: M Urban (urban@sun.ac.za)

1. Schoeman M, Apffelstaedt JP, Baatjes K, Urban M. Implementation of a breast cancer genetic service in South Africa – lessons learned. *S Afr Med J* 2013;103(8):529-533. [<http://dx.doi.org/10.7196/SAMJ.6814>]
2. Dandara C, Greenberg J, Lambie L, et al. Direct-to-consumer genetic testing: To test or not to test, that is the question. *S Afr Med J* 2013;103(8):510-512. [<http://dx.doi.org/10.7196/SAMJ.7049>]
3. Mayosi B, Flisher AJ, Lallo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. *Lancet* 2009;374(9693):934-947. [[http://dx.doi.org/10.1016/S0140-6736\(09\)61087-4](http://dx.doi.org/10.1016/S0140-6736(09)61087-4)]
4. Riley BD, Culver JO, Skrzyzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: Updated recommendations of the National Society of Genetic Counsellors. *J Genet Counsel* 2012;21(2):151-161. [<http://dx.doi.org/10.1007/s10897-011-9462-x>]
5. South African Government. Section 69, Consumer Protection Act 68. Pretoria: Government Press, 2008.

S Afr Med J 2013;103(8):517. DOI:10.7196/SAMJ.7232